REMARKS

Claims 15-22, 24-25, 27-34, 38-53, 56-62, 64, 66, 68 and 70 are now pending.

Final Status

Applicants submit the final status of the office action should be withdrawn in that claims 16, 18, 19 , 23, 25-34, 38-53, 56-62, 64, 68 and 70 have been rejected but no reasons have been given for the rejection. The reasons for rejecting these claims in the previous office action were rendered moot according to the language on pages 3 and 4 of the office action. If the claims stand rejected under a new rejection, Applicants have not had an opportunity to respond to this new rejection.

Claim Amendments After Final

If the final status of the office action is not withdrawn, applicants submit the amendments above are appropriate under 37 C.F.R. §1.116 and should be entered in that they do not raise new issues and in fact, reduce the issues to be presented on appeal. Claim 14 has been canceled and claims 15 and 16 have each been amended to incorporate the limitations of claim 14 to be in independent form. The amendment to claim 17 incorporates the limitations of cancelled claim 26 and the amendment to claim 20 incorporates the limitations of cancelled claim 23. These amendments direct method claims 15-22, 24-25, 27-34 to define preferred processes where the selective O-desulfation step is performed for a period of time of about 150 minutes.

The Priority Claim to Italian Application MI2000A000655:

Applicants acknowledge that the priority claim has been denied but will not formally withdraw the priority claim so that it is preserved for the claims in copending voluntary divisional application no. 11/030,156, filed January 7, 2005.

Non-Statutory Obviousness type Double patenting

The only outstanding rejection for which reasons have been provided in the final office action is the rejection of claims 14, 15, 17, 20-22 and 24 under the doctrine of non-

statutory obviousness type double patenting in view of claims 4-6 and 10 of copending application 10/240,606. A terminal disclaimer has not been filed in that it would not be effective against WO 01/72848 and Italian Application MI2000A000655.

Claims 16, 18, 19, 23, 25-34, 38-53, 56-62, 64, 66, 68 and 70 have not been included in this rejection and pending claims 17, 20-22 and 24 are no longer encompassed by this rejection after the amendment to claim 17 incorporating the limitations of claim 26. Therefore, the only pending claim to which this rejection applies is claim 15.

Claim 15

A feature which distinguishes the process for preparing K5 glycosaminoglycans described in claim 15 from the methods described in the '606 application (and WO 01/72848 and Italian Application MI2000A000655) is the selective O-desulfation step (step iv). This step comprises "treating the over sulfated product obtained at the end of step (iii) with a mixture of methanol/dimethyl sulfoxide for a period of time of about 150 minutes." The '606 application (and WO 01/72848 and Italian Application MI2000A000655) describes methods of preparing glycosaminoglycans but makes no reference to these specific conditions for the selective O-desulfation step employed. As discussed in the previous response, the '606 application (and WO 01/72848 and Italian Application MI2000A000655) discloses a broad range of time periods (1-8 hours) is suitable for the selective O-desulfation step. No preferred range is given and there is no disclosure for supporting a time period of about 150 minutes. The examples only provide for O-desulfation steps with a duration of 210 minutes (3.5 hours, Examples 1 and 2); 240 minutes(4 hours, Examples 3, 7 and 10); 120 minutes(2 hours, Examples 4 and 11) and 180 minutes (3 hours, Examples 5, 8 and 9). There is no suggestion of preferred time periods or that the duration of the O-desulfation reaction affects the structure (sulfate distribution) and ultimately the antithrombotic activity of the compounds produced. No mention is made of a 150 minute time period or a time period which approaches 150 minutes and there is no motivation to employ such a time period. Therefore, the methods of claim 15 are patentably distinct over the methods disclosed in the'606 application (and WO 01/72848 and Italian Application MI2000A000655).

The 132 declaration of Dr. Oreste of record further demonstrates the methods of claim 15 are patentably distinct over the methods disclosed in the'606 application (and WO 01/72848 and Italian Application MI2000A000655). The declaration illustrates there are significant unexpected advantages in preparing glycosaminoglycans under selected

conditions where the duration of the selective O-desulfation step is limited to 150 minutes such that the methods of claim 15, are clearly unobvious in view of the '606 application and WO 01/72848 and Italian Application MI2000A000655.

More particularly, Dr. Oreste indicated the results of the first experiment reported in the declaration showed (a) that the depolymerized products deriving from the partially O-desulfated product treated at 120 minutes and 180 minutes actually underwent a substantial loss of activity on all the coagulation parameters, (that on the antithrombin (Anti-IIa) activity being particularly severe), while the depolymerized products deriving from the partially O-desulfated product treated at 150 minutes maintained a good activity level on all the coagulation parameters, (that on the antithrombin (anti-IIa) activity being particularly high, i.e. about three times that of heparin).

Dr. Oreste also indicated the results of the second experiment were consistent with the first, showing that the depolymerized products deriving from the partially O-desulfated product treated at 180, 210 and 240 minutes underwent a loss of activity on all the coagulation parameters, while the depolymerized products deriving from the partially O-desulfated product treated at 150 minutes maintained a good activity level on all the coagulation parameters, (that on the antithrombin (anti-IIa) activity being at least of the same order of magnitude as that of the non-depolymerized parent product and very high *per se*, i.e. about four times as high as that of heparin)

This difference in activity level is significant and was unexpected. Based on what is known in the prior art about heparin, a correlation between the increase of activity and the elimination of a certain number of sulfate groups would have been expected in the kinetic study presented in the declaration. However, this did not happen. In evaluating the data presented in Tables 1 and 2 of Dr. Oreste's declaration it is evident that:

(i) the sulfate to carboxyl ratio of the sample with 150 minutes of selective O-desulfation is close to that of the 180 minute compound, but all the activities are markedly different (see Table 2);
(ii) in comparison with the 120 minute sample, the 150 minute sample contains less sulfate groups, i.e. it has a lower sulfate to carboxyl ratio, but the thrombin-related activities (anti-IIa and HCII), predictive of the antithrombotic activity, are markedly higher;
(iii) the 3-O sulfate groups on glucosamine of the 150 minute compound are less than those of the 120 minute compound and, therefore, its anti-Xa activity should be lower. Instead, it is higher;

(iv) the 150 minute compound contains almost the same amount of 3-O sulfate groups as that of the 180 minute compound on glucosamine, but it is more active.

The results obtained in the kinetic study presented in the declaration are not consistent with what one skilled in the art would have expected because the 150 minute sample does not have the same qualitative activity profile, with a more or less degree of activity, as the 120 minute and 180 minute samples. It was unexpected to find that, unlike heparin, the epimerized, sulfated K5 polysaccharide derivatives do not show any correlation between the sulfation degree and the biochemical activity.

Claims 16-22, 24-25, 27-34

While the outstanding rejection has not been applied to the methods defined by these claims, it should be noted these claims also recite the use of an O-desulfation reaction for a time period of about 150 minutes. Therefore, they clearly unobvious in view of the teachings within the '606 application and WO 01/72848 and Italian Application MI2000A000655 for the reasons indicated above for Claim 15.

Claims 38-53, 56-62, 64, 66, 68 and 70

As set forth in the 132 declaration of record of Dr. Oreste, the epimerized sulfated K5 polysaccharide derivatives of the present invention are complex molecules whose activity depends on the number and position of the sulfate groups and also on the adjacent residues. In particular, these compounds are semisynthetic polysaccharides which resemble the commercial heparin. The glycosaminoglycans of claims 38-53 are distinguished from those disclosed in the '606 application (and WO 01/72848 and Italian Application MI2000A000655) by the sulfation pattern defined by variables R, R_1, R_2 and R_3 of formula I, such that they not obvious in view of the disclosure within these applications. The compositions and treatment methods which employ them are also unobvious.

In view of the above, favorable reconsideration is courteously requested. If there are any remaining issues which can be expedited by a telephone conference, the examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Attorney Docket No.: **MARGI-0027-P01**

Date: **November 30, 2007**